PATENT SPECIFICATION

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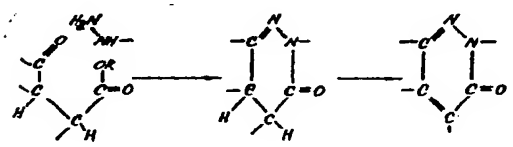
International Classification:—A61k. C07d.

COMPLETE SPECIFICATION

Process for the Manufacture of Pyridazone Compounds

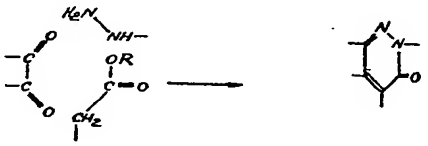
We, CIBA LIMITED, a body corporate organised according to the laws of Switzerland, of Basle, Switzerland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

It is known to make pyridazone-(3)-compounds by reacting a saturated or unsaturated λ-keto-carboxylic acid with a hydrazine and, if desired, oxidising the resulting pyridazinone. This process may be represented, for example, by the following scheme, in which R represents hydrogen or, for example, an alkyl group:—



An object of the present invention is to provide a new and advantageous process for making these compounds. In the process of the invention a hydrazine which contains at least three hydrogen atoms attached to the nitrogen atoms is condensed with two components, namely (a) an organic α-dicarbonyl-compound or a reactive functional carbonyl mono- or di- derivative thereof and (b) an organic carboxylic acid of which the carbon grouping in the α-position is a reactive methylene group or a reactive nitrogen-free functional derivative of such acid directly or in stages, the ring-closure being brought about by the use of a basic condensing agent.

The new process is distinguished in that it synthesizes the pyridazine ring from three simple bridge members and is therefore capable of wide variation with regard to the substituents. Furthermore, in most cases very good yields are obtained. The process may be represented, for example, as follows:—



As hydrazines there are used more especially hydrazine itself or, for example, monoalkyl-hydrazines such as methyl-hydrazine, monoaryl-hydrazines such as phenyl-hydrazines or monoheterocyclyl-hydrazines such as pyridyl-hydrazines, if desired, in the form of their salts.

Among organic α-dicarbonyl-compounds there are to be understood α-diketones such as diacetyl, benzils or pyridils, α-keto-aldehydes such as alkyl- or aryl- glyoxals, for example, methyl- or phenyl-glyoxal, or glyoxal itself or o-quinones. Reactive functional carbonyl mono- or di-derivatives are acetals, thioacetals, ketals, thioketals, acylates, bisulphite compounds or oximes.

The organic carboxylic acids are advantageously reacted in the form of their reactive nitrogen-free functional derivatives, especially their esters with lower alkanols. It is of advantage to use those acid esters in which the α-methylene group is activated by a carbonyl, carboxyl or carbalkoxy or cyano group, for example, acyl-acetic acid esters such as aceto- or benzoyl-acetic acid esters, cyanoacetic acid esters or malonic acid esters. Further suitable acid esters are, for example, aryl- or heterocyclylacetic acid esters such as phenyl-acetic acid esters or pyridyl-acetic acid esters, glycollic acid esters or acylamino-acetic acid esters, such as hippuric acid esters.

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The reactions may be carried out in the absence, but advantageously in the presence, of solvents at ordinary or raised temperature in an open vessel or a closed vessel under pressure. As basic condensing agents there are used more especially alkaline compounds, such as hydroxides, alcoholates, hydrides, amides or hydrocarbon compounds of alkali metals or alkaline earth metals, for example, those of sodium or potassium, or strong organic bases such as tertiary amines or quaternary ammonium hydroxides, for example, triethylamine or trimethylbenzyl - ammonium hydroxide.

The process may be carried out in stages, for example, by first condensing the hydrazine with the organic α-dicarbonyl-compound or derivative thereof to form a monohydrazone. The latter is then reacted in a second stage with the carboxylic acid or derivative thereof to form the pyridazone-(3) compound, using a basic condensing agent. The condensing agent may be added immediately or after the formation of the corresponding acylhydrazones.

In another method of carrying out the process in stages a carboxylic acid hydrazide is first formed from the organic carboxylic acid of the above kind and the hydrazine, and the product is condensed in a second stage with the dicarbonyl-compound or derivative thereof, using a basic condensing agent. In this case also the condensing agent may be added immediately or after the formation of the acylhydrazones.

A third alternative is to carry out the reaction in the presence of all three reaction components and the basic condensing agent at the same time. Thus, for example, hydrazine may be reacted with cyanacetic acid ester and benzil in the presence of an alkaline condensing agent to form 4-cyano-5:6-diphenyl-pyridazone-(3) directly.

When compounds are obtained which contain a functionally converted carboxyl group in 4-position, such as the nitrile group or an esterified carboxyl group, such group may be hydrolysed in the usual manner into a free carboxyl group. If desired, a free carboxylic acid group in 4-position may be decarboxylated in known manner, for example, by the action of heat.

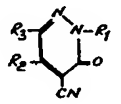
Furthermore a pyridazone-(3) having a hydrogen atom bound to the ring nitrogen in 2-position so obtained may be alkylated at any stage in the process advantageously by reaction with a reactive ester of an alcohol, such as a dialkyl sulphate or an alkyl halide.

When the compounds of the invention contain basic or acid groups, their salts with acids or bases may be prepared from them in the usual manner.

The starting materials are known or can be made by methods in themselves known.

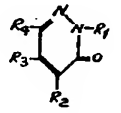
The invention extends to any modification of the process in which there is used as starting material a compound obtainable as an intermediate product at any stage in the process, and the remaining steps of the process are carried out.

Pyridazone-(3)-compounds having a cyano group in the 4-position possess valuable pharmacological properties and can be used as medicaments. They have an analgesic action. Especially valuable in this respect are compounds of the formula:—



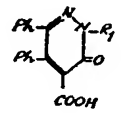
in which R_1 represents hydrogen or a phenyl or lower alkyl residue, and R_2 and R_3 represent phenyl or lower alkyl residues. On account of their analgesic action there may be mentioned principally 2:5:6-tri-lower alkyl-4-cyano-pyridazone-(3)-compounds, more especially 2:5:6-trimethyl-4-cyano-pyridazone-(3).

Pyridazone-(3)-compounds of the formula:



in which R_1 represents hydrogen or a phenyl or lower alkyl residue, R_2 represents a free or esterified carboxyl group or an acetyl group, and in which R_3 and R_4 represent phenyl or lower alkyl residues or R_3 represents a lower alkyl residue or hydrogen and R_4 represents hydrogen, can be used as intermediate products for the preparation of the above mentioned nitriles by converting the substituent in 4-position into the cyano group by methods in themselves known, for example, by conversion into the carbamoyl group and then splitting off water. Compounds having this formula can also be converted by methods in themselves known into the corresponding 4-aminopyridazone-(3)-compounds, which include analgesics, anaesthetics and chemotherapeutics.

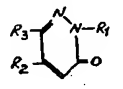
Compounds of the formula:—



in which R_1 represents a phenyl or lower alkyl residue and the symbols Ph stands for phenyl residues, are also valuable as solution promoters. They are excellent solution promoters, for example, for medicaments of the pyrazolone series which are sparingly soluble or insoluble in water, such as 1-phenyl-2:3-

dimethyl - 4 - dimethylamino - pyrazolone. 2 - Methyl - 4 - carboxy - 5 : 6 - diphenyl-pyridazone-(3) may be specially mentioned. Aqueous solutions of medicaments comprising these compounds can be prepared in the usual manner.

4 : 5 : 6-triphenyl-pyridazone-(3), 4-benzoyl-5 : 6-diphenyl-pyridazone-(3), and pyridazone-(3)-compounds having the formula:—



in which R_1, R_2 and R_3 represent phenyl or lower alkyl residues, containing 1—5 carbon atoms, possess antibacterial properties and can be used as medicaments or disinfectants.

In the above description and appendant claims the lower alkyl residues contain 1—5 carbon atoms and represent for example ethyl, propyl, butyl, amyl, and more especially methyl residues; the phenyl residues are unsubstituted phenyl residues or phenyl residues substituted by halogen atoms, and esterified carboxyl groups are especially for example carbalkoxy groups containing lower alkyl residues containing 1—5 carbon atoms.

The new pharmacologically active compounds of the kind mentioned above may be used as medicaments in the form of pharmaceutical preparations, which comprise the new compound or a salt thereof in admixture with a pharmaceutical organic or inorganic carrier suitable for enteral, parenteral or topical administation, such carrier advantageously consisting at least partly of organic or solid inorganic matter. For the formation of the carrier there come into consideration such substances as do not react with the new compounds such, for example, as water, gelatine, lactose, starch, magnesium stearate, talc, vegetable oils, benzyl alcohols, gum, polyalkylene glycols, vaseline (Registered Trade Mark), cholesterine or other known medicinal carriers. The pharmaceutical preparations may be, for example, in the form of tablets, dragees, ointments, creams or in liquid form as solutions, suspensions or emulsions. If desired, they may be sterilised and/or contain adjuvants, such as preservatives, stabilizers, wetting agents or emulsifying agents, salts for regulating the osmotic pressure or buffers. They may also contain other therapeutically valuable substances. Especially valuable are pharmaceutical preparations suitable for oral administration, for example, tablets. These pharmaceutical preparations are prepared by methods in themselves known.

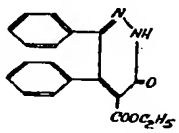
N-unsubstituted pyridazone-(3)-compounds are tautomeric with 3-oxy-pyridazines. Such compounds are deliberately represented herein as having the structure of pyridazones.

The following Examples illustrate the invention including the optional saponification, esterification, decarboxylation or alkylation of the products obtained by the above described condensation reaction, the parts being by weight unless otherwise stated, and the relationship of parts by weight to parts by volume being the same as that of the gram to the cubic centimetre:—

EXAMPLE 1

10 parts of benzil are introduced into 50 parts by volume of ethyl alcohol and mixed, while cooling with ice water, with 3 parts of hydrazine hydrate. In order to complete the reaction the mixture is heated for a further ½ hour at 60°C., then allowed to cool and filtered with suction to remove the precipitate. In this manner there is obtained the monohydrazone of benzil in the form of white crystals melting at 151°C.

10 parts of benzil monohydrazone and 10 parts of malonic acid diethyl ester are introduced into a sodium ethylate solution prepared from 2 parts of sodium and 200 parts by volume of ethyl alcohol, and the mixture is heated for 3 hours in a bath having a temperature of 90°C. The mixture is allowed to cool, a small amount of impurities is filtered off with suction, and the alcohol is evaporated under reduced pressure. The residue is dissolved in a small quantity of water, the solution is adjusted to a pH value of 5—6 by means of 2N-hydrochloric acid, and the white precipitate is filtered off. After recrystallisation from boiling benzene there is obtained 4-carbethoxy-5 : 6-diphenyl-pyridazone-(3) of the formula:



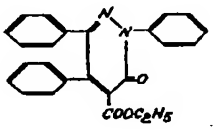
in the form of white crystals melting at 219—220°C.

EXAMPLE 2

210 parts of benzil are dissolved in 700 parts by volume of ethyl alcohol and slowly mixed with 103 parts of phenyl-hydrazine. Yellowish crystals soon separate out, and are recrystallised from boiling ethyl alcohol. The resulting benzil monophenyl-hydrazone melts at 135°C.

30 parts of the monophenyl-hydrazone of benzil are heated with 20 parts of malonic acid diethyl ester and 2 parts of sodium alcoholate under reflux for 48 hours in a bath having a temperature of 160—170°C. In order to remove the excess of malonic ester the reaction mixture is extracted with 250 parts by volume of petroleum ether, and the undissolved residue is taken up in 200 parts by volume of boiling ethyl alcohol. Upon cooling,

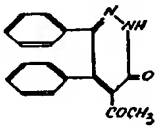
4 - carbethoxy - 2:5:6 - triphenyl - pyridazone-(3) of the formula: —



precipitates in the form of a yellow precipitate, which melts at 184°C. after being again crystallised from boiling ethyl alcohol.

EXAMPLE 3

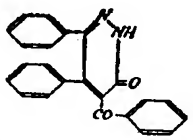
23 parts of benzil monohydrazone and 16 parts of ethyl acetoacetate are added to a solution of 2.5 parts of sodium in 150 parts by volume of ethyl alcohol. The mixture is heated for 3 hours in a bath having a temperature of 90°C., then it is allowed to cool, filtered with suction to remove a small amount of impurities, and the filtrate is evaporated to dryness *in vacuo*. The residue is taken up in a small quantity of water, the solution is given a pH value of 5—6 by means of 2N-hydrochloric acid, whereupon a yellow product precipitates which is recrystallised from boiling ethyl alcohol. In this manner there is obtained 4-acetyl-5:6-diphenyl-pyridazone-(3) of the formula: —



in the form of pale yellowish crystals melting at 232—233°C.

EXAMPLE 4

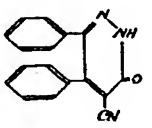
2.5 parts of sodium are dissolved in 250 parts by volume of ethyl alcohol and, when the formation of sodium alcoholate is complete, 23 parts of benzil monohydrazone and 24 parts of ethyl benzoyl-acetate are added. The mixture is then heated for 3 hours at a bath temperature of 90°C., and then allowed to cool, filtered and evaporated. The residue is taken up in a little water, and the solution is adjusted to a pH value of 5—6. The yellow precipitate, which separates out, is crystallised from a small quantity of ethyl alcohol and there is obtained 4-benzoyl-5:6-diphenyl-pyridazone-(3) of the formula: —



in the form of pale yellowish crystals melting at 224—225°C.

EXAMPLE 5

1.25 parts of sodium are introduced into 200 parts by volume of ethyl alcohol. When all the sodium has reacted, 11.5 parts of benzil monohydrazone and 7 parts of ethyl cyanacetate are added, the whole is heated for 3 hours at a bath temperature of 90°C., then allowed to cool and filtered with suction in order to remove impurities which have separated out. The filtrate is evaporated to dryness *in vacuo*, the residue is taken up in a small amount of water, and the solution is adjusted to a pH value of 5—6. The precipitate which separates out is recrystallised from ethyl alcohol. There is obtained 4-cyano-5:6-diphenyl-pyridazone-(3) of the formula: —

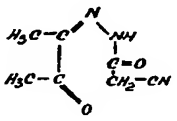


in the form of white crystals melting at 274—275°C.

EXAMPLE 6

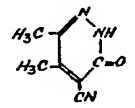
40 parts of hydrazine hydrate are introduced dropwise into a solution of 90 parts of methyl cyanacetate in 450 parts by volume of ethyl alcohol while cooling with ice water. The whole is allowed to stand for one hour at room temperature, and then filtered with suction to separate the cyanacetic acid hydrazide which precipitates in the form of white crystals melting at 115°C.

22 parts of diacetyl are dissolved in 150 parts by volume of ethyl alcohol and slowly mixed with 24 parts of cyanacetic acid hydrazide, whereupon the solution heats up slightly and a white crystalline precipitate is soon formed. After 2 hours, the resulting diacetyl monocyanacetyl hydrazone of the formula: —



is separated by filtering with suction. The product melts at 133—134°C. after recrystallisation from benzene.

2.5 parts of diacetyl-mono- cyanacetyl-hydrazone are introduced into a solution of 0.7 part of sodium in 50 parts by volume of ethyl alcohol, and the whole is heated for 3 hours at a bath temperature of 90°C. The mixture is filtered with suction while hot to remove impurities, the filtrate is evaporated, the residue is taken up in a small amount of water, and adjusted to a pH value of 5—6 with 2N-hydrochloric acid. 4-Cyano-5:6-dimethyl-pyridazone-(3) of the formula: —

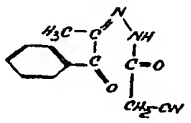


precipitates out, and is again crystallised from ethyl alcohol. There are obtained white crystals melting at 211—212°C.

EXAMPLE 7

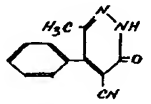
30 parts of benzoyl-acetyl are dissolved in 200 parts by volume of ethyl alcohol, and the solution is slowly mixed, while cooling with ice water, with 20 parts of cyanacetic acid hydrazide. The mixture is allowed to stand for 2 hours at room temperature and then filtered with suction to separate the white precipitate.

By recrystallisation from boiling ethyl alcohol benzoyl - acetyl - mono - cyanacetyl-hydrazone of the formula: —



is obtained in the form of white crystals melting at 169—170°C.

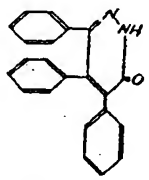
22 parts of benzoyl-acetyl-mono-cyanacetyl-hydrazone are added to a solution if sodium ethylate prepared from 2.3 parts of sodium and 300 parts by volume of ethyl alcohol, the mixture is allowed to stand for one hour at room temperature, and then heated for 3 hours at a bath temperature of 90°C. The whole is allowed to cool, evaporated to dryness, and the residue is taken up in a small amount of water, and the solution is given a pH value of 5—6 by means of 2N-hydrochloric acid, whereupon a white precipitate is formed which is recrystallised from boiling ethyl alcohol. There is obtained 4-cyano-5-phenyl-6-methyl-pyridazone-(3) of the formula: —



in the form of white crystals melting at 199—200°C.

EXAMPLE 8

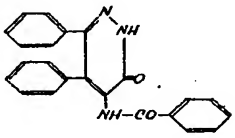
20 parts of benzil monohydrazone and 20 parts of ethyl phenyl-acetate are added to a sodium ethylate solution prepared from 4 parts of sodium and 250 parts by volume of ethyl alcohol. The mixture is allowed to stand for one hour at room temperature, and is then heated for 3 hours at a bath temperature of 100°C. The whole is allowed to cool, then filtered with suction to remove impurities which precipitate, and the filtrate is evaporated to dryness *in vacuo* and the residue is taken up in water. The aqueous solution is given a pH value of 5—6 by means of 2N-hydrochloric acid, whereupon a white crystalline precipitate is formed which is recrystallised from benzene. The resulting 4:5:6-triphenyl-pyridazone-(3) of the formula: —



is obtained in the form of white crystals melting at 272—273°C.

EXAMPLE 9

9 parts of benzil monohydrazone and 10 parts ethyl hippurate are introduced into a solution of 1 part of sodium in 200 parts by volume of absolute ethyl alcohol. The mixture is then allowed to stand for one hour at room temperature, and is subsequently heated for three hours at a bath temperature of 90°C. After being cooled, the mixture is evaporated to dryness, the residue is extracted with water, and the solution is adjusted to a pH value of 5—6 with 2N-hydrochloric acid. In this manner there is obtained a white precipitate which is recrystallised from benzene. The resulting 4 - benzoylamino - 5:6 - diphenyl-pyridazone-(3) of the formula: —



melts at 232—233°C.

EXAMPLE 10

10 parts of benzil, 7 parts of ethyl cyanacetate and 2.4 parts of hydrazine hydrate are introduced into a solution of 1.3 parts of sodium in 100 parts by volume of anhydrous ethyl alcohol. The whole is stirred for one hour at room temperature, and is then heated for 3 hours at a bath temperature of 90°C. Impurities are then filtered off with suction, the filtrate is evaporated, the residue is dissolved in water, and the solution is given a pH value of 5—6 and filtered with suction to separate the white precipitate. After recrystallisation from ethyl alcohol there is obtained a product melting at 274—275°C. which is identical with the 4-cyano-5:6-diphenyl-pyridazone-(3) obtained as described in Example 5.

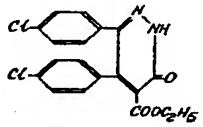
EXAMPLE 11

4 parts of hydrazine hydrate are introduced into a solution of 9 parts of ethyl cyanacetate in 100 parts by volume of anhydrous ethyl alcohol. There are then added 8 parts of di-

acetyl and a solution of 4 parts of sodium in 100 parts by volume of anhydrous ethyl alcohol. The reaction mixture is heated for 4 hours, while stirring well, at 90° C. The mixture is then evaporated to dryness, the residue is taken up in 200 parts by volume of water, given a pH value of 6—7 with 2N-hydrochloric acid, and filtered to remove the precipitate. By recrystallisation from boiling ethyl alcohol there is obtained a product melting at 211—212° C., which is identical with the 4-cyano-5:6-dimethyl - pyridazone - (3) described in Example 6.

EXAMPLE 12.

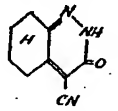
2.3 parts of sodium, dissolved in 400 parts by volume of absolute ethyl alcohol, are heated with 20 parts of ethyl malonate and 29.3 parts of para-para'-dichlorobenzil monohydrazone for 4 hours at 90° C. while stirring. The mixture is evaporated to dryness, and the residue is dissolved in 800 parts by volume of a 1N-solution of caustic soda. The solution is given a pH value of 6—7 with 2N-hydrochloric acid, and the precipitate is filtered off with suction. By recrystallisation from boiling ethyl alcohol there is obtained 5:6-di-(para-chlorophenyl)-4-carbethoxy-pyridazone-(3) of the formula



in the form of white crystals melting at 235—236° C.

EXAMPLE 13.

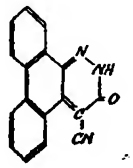
18 parts of 1:2-cyclohexanedione are dissolved in 200 parts by volume of absolute ethyl alcohol, then mixed with 13 parts of cyanacetic acid hydrazide, stirred for 2 hours at room temperature, then a solution of 4 parts of sodium in 200 parts by volume of absolute ethyl alcohol is added, and the whole is heated at 90° C. for 3 hours. The reaction solution is evaporated to dryness, the residue is taken up in 400 parts by volume of water, and the pH value is adjusted to 6—7 with 2N-hydrochloric acid, whereby a yellow product is precipitated which is recrystallised from boiling ethyl alcohol. There is obtained in this manner 5:6-cyclohexano - 4 - cyano-pyridazone-(3) of the formula



in the form of yellowish crystals melting at 240—241° C.

EXAMPLE 14.

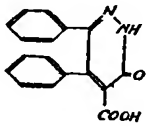
10 parts of 9:10-phenanthrene-quinone are introduced into 500 parts by volume of absolute ethyl alcohol. The suspension is mixed with 4.8 parts of cyanacetic acid hydrazide and 1 part by volume of piperidine, while stirring well, and the whole is heated for one hour at 90° C. A small amount of an undissolved precipitate is filtered off while hot. Upon cooling a yellow product precipitates, which is recrystallised from boiling ethyl alcohol. In this manner there is obtained 5:6-(9¹:10¹-phenanthreno) - 4 - cyano-pyridazone-(3) of the formula



in the form of yellow crystals melting at 290° C. with decomposition.

EXAMPLE 15.

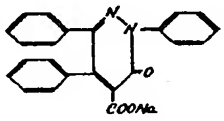
3 parts of 4-carbethoxy - 5:6 - diphenyl-pyridazone-(3) are heated with 100 parts by volume of 2N-caustic soda solution at 110° C. for 2 hours in an oil bath. After cooling, the mixture is rendered acid to Congo with 10N-hydrochloric acid, while cooling, whereupon a white precipitate is formed, which is recrystallised from a small amount of boiling ethyl alcohol. 4-Carboxy-5:6-diphenyl-pyridazone-(3) of the formula



is obtained in the form of white crystals melting at 243—244° C. (with decarboxylation).

EXAMPLE 16.

10 parts of 4-carbethoxy-2:5:6-triphenyl-pyridazone-(3) are introduced into 250 parts by volume of a 2N-solution of caustic soda, and the whole is heated for 12 hours at the boil. A small amount of undissolved starting material is filtered off with suction while hot, and the filtrate is evaporated to 100 parts by volume, whereby a white precipitate is formed, which is recrystallised from boiling ethyl alcohol. In this manner there is obtained the sodium salt of 4-carboxy-2:5:6-triphenyl-pyridazone-(3) of the formula

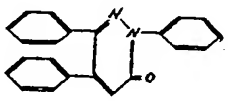


in the form of white crystals melting at 285—286° C. By dissolving the sodium salt in

water and acidifying the solution with 2N-hydrochloric acid, 4-carboxy-2:5:6-triphenyl-pyridazone-(3) melting at 248°C. (with decarboxylation) precipitates.

EXAMPLE 17

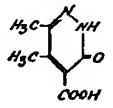
1 part of 4-carboxy-2:5:6-triphenyl-pyridazone-(3) is heated in a flask over an open flame until the evolution of gas has ceased. The oily residue is crystallised from boiling ethyl alcohol, and there is obtained 2:5:6-triphenyl-pyridazone-(3) of the formula:—



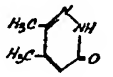
in the form of white crystals melting at 233—234°C.

EXAMPLE 18

32 parts of 4-cyano-5:6-dimethyl-pyridazone-(3) are heated in 300 parts by volume of sulphuric acid of 90 per cent. strength at 150°C. (external temperature) for 12 hours. The reaction solution after being cooled, is mixed with 700 parts of ice, and the mixture is adjusted to a pH value of 3 with a 10N-solution of caustic soda, while cooling well. The mixture is then evaporated to dryness, and the residue is extracted with hot chloroform. The residue from the chloroform extract is recrystallised from a small amount of ethyl alcohol and in this manner 4-carboxy-5:6-dimethyl-pyridazone-(3) of the formula:



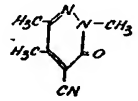
is obtained in the form of white crystals melting at 172—173°C. 1 part of 4-carboxy-5:6-dimethyl-pyridazone-(3) obtained as above is heated in an oil bath having a temperature of 200°C. After 10 minutes the evolution of carbon dioxide ceases, and the residue is solidified by cooling. By recrystallisation from a small amount of ethyl alcohol there is obtained 5:6-dimethyl-pyridazone-(3) of the formula:—



in the form of white crystals melting at 220—221°C.

EXAMPLE 19

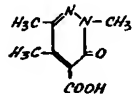
15 parts of 4-cyano-5:6-dimethyl-pyridazone-(3) are dissolved in 50 parts by volume of a 2N-solution of caustic soda and slowly mixed in 3 portions with 13 parts of dimethyl sulphate, whereby a crystalline product precipitates, and the latter is filtered off with suction. By recrystallisation from petroleum ether there is obtained 4-cyano-2:5:6-trimethyl-pyridazone-(3) of the formula:—



in the form of white crystals meling at 114—115°C.

EXAMPLE 20

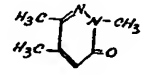
20 parts of 4-cyano-2:5:6-trimethyl-pyridazone-(3) are heated with 200 parts by volume of sulphuric acid of 90 per cent. for 12 hours in an oil bath having a temperature of 150°C. After cooling the mixture, it is poured on to 700 parts of ice, the pH value is adjusted to 3 while cooling, the mixture is evaporated to dryness, and the residue is extracted with hot chloroform. The residue from the chloroform extract is recrystallised from a small amount of ethyl alcohol, whereby 4-carboxy-2:5:6-trimethyl-pyridazone-(3) of the formula:—



is obtained in the form of white crystals melting at 107—108°C.

EXAMPLE 21

2 parts of 4-carboxy-2:5:6-trimethyl-pyridazone-(3) are heated for 10 minutes in an oil bath having a temperature of 220°C. After cooling the mixture, the residue is crystallised from a large quantity of petroleum ether, and there is obtained 2:5:6-trimethyl-pyridazone-(3) of the formula:—

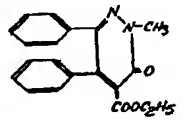


in the form of crystals melting at 92—93°C.

EXAMPLE 22

16 parts of 4-carbethoxy-5:6-diphenyl-pyridazone-(3), dissolved in a mixture of 50 parts by volume of a 1N-solution of caustic potash and 100 parts by volume of methanol, are slowly mixed with 5 parts by volume of dimethyl sulphate during which the solution heats up slightly. It is then heated at the boil for 30 minutes, the solution is evaporated *in vacuo*, and the residue is extracted by agitation with ether and water. After drying the extract over potassium carbonate and evaporating the

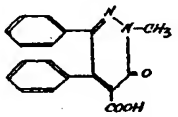
ether, the residue is recrystallised from alcohol, and 2 - methyl - 4 - carbethoxy - 5:6-diphenyl-pyridazone-(3) of the formula:—



is obtained in the form of white crystals melting at 146—147°C.

EXAMPLE 23

18.4 parts of 2-methyl-5:6-diphenyl-4-carbethoxy-pyridazone-(3) are boiled, under reflux, in a mixture of 120 parts by volume of 0.5N-caustic soda solution and 240 parts by volume of alcohol for 3 hours. Upon cooling handsome needles are formed. The mixture is evaporated to dryness, the residue is dissolved in warm water, and the solution is acidified with hydrochloric acid to such an extent as to turn Congo red. The precipitated 2-methyl-4-carboxy-2:5-diphenyl-pyridazone-(3) of the formula:—



is recrystallised from alcohol and melts at 222°C.

It can be used, for example, as a solution promoter as follows:—

10 parts of 1-phenyl-2:3-dimethyl-4-dimethylamino-pyrazolone and 10 parts of 2-methyl - 4 - carboxy - 5:6 - diphenyl-pyridazone-(3) are heated together with 80 parts by volume of water, whereby a solution is formed which remains clear after cooling.

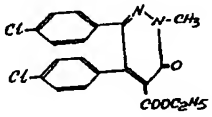
EXAMPLE 24

5.5 parts of 2-methyl-5:6-diphenyl-4-carboxy-pyridazone-(3) are slowly heated to 220—230°C. and maintained at that temperature for 30 minutes. The decarboxylation is then complete and the resulting 2-methyl-5:6-diphenyl-pyridazone-(3) of the formula:—

melts at 154-156°C.

EXAMPLE 25

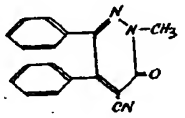
3.9 parts of 5:6-bis-(para-chlorophenyl)-4-carbethoxy-pyridazone-(3), dissolved in 10 parts by volume of a 1N-solution of caustic potash and 20 parts by volume of methanol, are mixed with 1 part by volume of dimethyl sulphate, while hot and while stirring. The whole is boiled for a further 30 minutes, evaporated to dryness, the residue is extracted by agitation with ether and water, the ethereal extract is crystallised from alcohol, and there is obtained 2-methyl-5:6-bis-(para-chlorophenyl)-4-carbethoxy-pyridazone-(3) of the formula:—



in the form of crystals melting at 169—170°C.

EXAMPLE 26

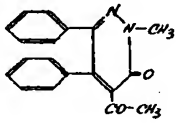
8.8 parts of 4-cyano-5:6-diphenyl-pyridazone-(3), dissolved in a mixture of 32.2 parts by volume of a 1N-solution of caustic potash and 100 parts by volume of water, are mixed dropwise with 5 parts by volume of dimethyl sulphate while hot and while stirring. There is immediately formed a dense yellow precipitate. The resulting 2-methyl-5:6-diphenyl-4-cyano-pyridazone-(3) of the formula:—



is isolated on a suction filter, and recrystallised from 500 parts of alcohol. It melts at 211—212°C.

EXAMPLE 27

17 parts of 4-acetyl-5:6-diphenyl-pyridazone-(3), dissolved in a mixture of 60 parts by volume of a 1N-solution of caustic potash and 200 parts by volume of water are mixed, while stirring in the warm, dropwise with 10 parts by volume of dimethyl sulphate. The mixture is then boiled for 30 minutes. The filter residue is recrystallised from alcohol, and in this manner there is obtained 2-methyl-5:6-diphenyl - 4 - acetyl - pyridazone - (3) of the formula:—

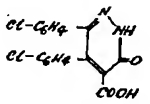


in the form of crystals melting at 158—159°C.

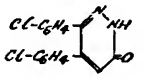
EXAMPLE 28

17.6 parts of 5:6-bis-(para-chlorophenyl)-4-carbethoxy-pyridazone-(3) are boiled for 6 hours with 300 parts by volume of a 1N-solution of caustic soda. The solution is then given a pH value of 3 with dilute hydrochloric acid, and the precipitate so obtained is crystallised from dioxane of 50 per cent. strength. The resulting 5:6-bis-(para-chloro-

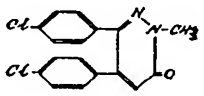
phenyl) - 4 - carboxy - pyridazone - (3) of the formula: —



melts with decomposition at 274°C. 1 part of 5:6 - bis - (para - chlorophenyl) - 4 - carboxy-pyridazone-(3) is heated in an oil bath for 15 minutes at 275—285°C. The melt so obtained is recrystallized twice from a mixture of 4 parts by volume of alcohol and 2 parts by volume of water on each occasion. The resulting 5:6 - bis - (para - chlorophenyl) - pyridazone-(3) of the formula: —



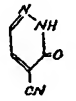
melts at 202°C. 6.34 parts of 5:6-bis-(para-chlorophenyl)-pyridazone-(3) are dissolved in 20 parts by volume of 1N-caustic potash solution and 40 parts by volume of methanol. 2.4 parts by volume of dimethyl sulphate are introduced dropwise into the solution in the hot while stirring, and the whole is then heated for 15 minutes at the boil. The methanol is then evaporated, and the residue is extracted with water and ether. After drying and evaporating the ethereal solution, the resulting 2-methyl - 5:6 - bis - (para - chlorophenyl)-pyridazone-(3) of the formula: —



is distilled at 220°C. under 0.2 mm pressure of mercury. After cooling, there is formed an amorphous white mass which cannot be obtained in a crystalline form from the usual solvents. The compound melts unsharply at about 75°C.

EXAMPLE 29

295 parts of glyoxal-sodium bisulphite are stirred in 1000 parts by volume of water, and slowly mixed with a solution of 99 parts of cyanacetic acid hydrazide in 1000 parts by volume of ethyl alcohol. The mixture is rendered alkaline with 10N-caustic soda solution and stirred for 2 hours, the solution becoming slightly warm. To complete the reaction the whole is stirred for a further half hour at 60°C., adjusted to a pH value of 3 with hydrochloric acid, and evaporated to dryness *in vacuo*. The residue is extracted with chloroform in a soxhlet apparatus. After evaporating the chloroform, the product is recrystallised from a little ethyl alcohol and there is obtained 4-cyano-pyridazone-(3) of the formula: —



in the form of white crystals melting at 184—185°C.

EXAMPLE 30

12.1 parts of 4-cyano-pyridazone-(3) are heated in 100 parts by volume of sulphuric acid of 85 per cent. strength for 8 hours at 140°C. After being cooled, the reaction solution is poured onto 400 parts of ice and, while cooling well, adjusted to a pH value of 3 with 10N-caustic soda solution. The whole is then evaporated to dryness, and the residue is extracted with hot chloroform. After evaporating the chloroform, the product remaining behind is recrystallised from a little boiling ethyl alcohol. There is obtained 4-carboxy-pyridazone-(3) of the formula: —

in the form of white crystals melting at 199—200°C.

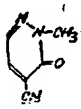
EXAMPLE 31

1.4 parts of 4-carboxy-pyridazone-(3) are heated in a distilling flask over an open flame, during which decarboxylation takes place and a liquid passes over which solidifies in the receiver. The product is crystallised from boiling ligroin and there is obtained pyridazone-(3) of the formula: —

in the form of white crystals melting at 103—104°C. In the air the product takes up one mol of water of crystallisation and the melting point drops to 70—73°C.

EXAMPLE 32

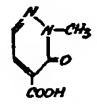
12 parts of 4-cyano-pyridazone-(3) are dissolved in 50 parts by volume of 2N-caustic soda solution, and slowly mixed with 13 parts of dimethyl sulphate in three portions, whereby a crystalline product is precipitated which is filtered off with suction. By recrystallisation from ligroin there is obtained 2-methyl-4-cyano-pyridazone-(3) of the formula: —



in the form of white crystals melting at 130—131°C.

EXAMPLE 33

20 parts of 2-methyl-4-cyano-pyridazone-(3) are heated with 200 parts by volume of sulphuric acid of 85 per cent. strength for 12 hours in an oil bath at 150°C. After being cooled, the whole is poured on to 700 parts of ice, adjusted to a pH value of 3 while cooling, evaporated to dryness and extracted with hot chloroform. The chloroform residue is recrystallized from a little ethyl alcohol, whereby 2-methyl-4-carboxy-pyridazone-(3) of the formula:—



is obtained in the form of white crystals melting at 125—126°C.

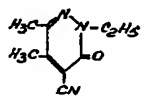
EXAMPLE 34

2 parts of 2-methyl-4-carboxy-pyridazone-(3) are heated in an oil bath at 240°C. for 10 minutes. After cooling, the residue is crystallised from petroleum ether and there is obtained 2-methyl-pyridazone-(3) of the formula:—

in the form of white deliquescent crystals melting at 38—39°C.

EXAMPLE 35

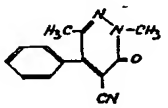
15 parts of 4-cyano-5:6-dimethyl-pyridazone-(3) are dissolved in 50 parts by volume of 2N-caustic soda solution and slowly mixed with 15 parts of diethyl sulphate in three portions. The whole is left to stand for one hour at room temperature, and 15 parts by volume of 2N-caustic soda solution are then added. After four hours the reaction solution is extracted with 300 parts by volume of chloroform and the chloroform residue distilled. At 140—142°C. under 0.1 mm pressure of mercury 2-ethyl-4-cyano-5:6-dimethyl-pyridazone-(3) of the formula:—



passes over and crystallises in the receiver. The product is recrystallised from petroleum ether and obtained in the form of white crystals melting at 66—67°C.

EXAMPLE 36

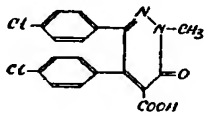
9 parts of 4-cyano-5-phenyl-6-methyl-pyridazone-(3) are dissolved in 22 parts by volume of 2N-caustic soda solution and slowly mixed with 6 parts of dimethyl sulphate in three portions, whereby a crystalline product precipitates which is filtered with suction. By recrystallisation from a little boiling ethyl alcohol there is obtained 2:6-dimethyl-4-cyano-5-phenyl-pyridazone-(3) of the formula:



in the form of white crystals melting at 187—188°C.

EXAMPLE 37

10 parts of 2-methyl-5:6-bis-(para-chlorophenyl)-4-carbethoxy-pyridazone-(3) are boiled with 100 parts by volume of 0.5N-caustic soda solution and 100 parts by volume of alcohol for 2 hours under reflux. The alcohol is then evaporated *in vacuo*, the concentrate diluted with warm water, the solution clarified by filtration and precipitated whilst still warm while stirring with dilute hydrochloric acid. The 2-methyl-5:6-bis-(para-chlorophenyl)-4-carboxy-pyridazone-(3) of the formula:—



is filtered off with suction and recrystallised from dilute alcohol. It melts at 241—242°C.

EXAMPLE 38

5 parts of 2-methyl-5:6-bis-(para-chlorophenyl)-4-carboxy-pyridazone-(3) are decarboxylated by being heated for 15 minutes at 250°C. The resulting 2-methyl-5:6-bis-(para-chlorophenyl)-pyridazone-(3) is purified by distillation as described in Example 28.

EXAMPLE 39

The 2:5:6-trimethyl-4-cyano-pyridazone-(3) described in Example 19 is made up in the usual manner into a pharmaceutical preparation of the following composition:—

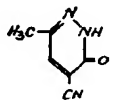
100 mg 2:5:6-trimethyl-4-cyano-pyridazone-(3)
65 mg lactose
2 mg gelatine
65 mg starch
1 mg magnesium stearate
17 mg talcum

250 mg

EXAMPLE 40

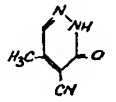
50 parts by volume of aqueous methylglyoxal solution of 41 per cent. strength are mixed with 150 parts by volume of sodium hydrosulphite solution of 40 per cent. strength. To the resulting solution are then added 27

parts of cyanacetic acid hydrazide, the pH is adjusted to 9—10 with 10N-caustic soda solution, and the solution is heated to 70°C. for 1 hour, then allowed to cool, and the pH adjusted to 4—5 with concentrated hydrochloric acid. The red solution is extracted by agitating it with a large amount of warm chloroform several times, and the chloroform solution is evaporated. The residue is extracted with a small amount of boiling benzene, a portion of the residue dissolving readily and precipitating again on cooling after filtration. The precipitate is recrystallized several times from boiling benzene. There is obtained 4-cyano - 6 - methyl - pyridazone-(3) of the formula:



in the form of white crystals melting at 166—167°C.

The portion which is sparingly soluble in benzene is recrystallized from ethyl alcohol to yield 4-cyano-5-methyl-pyridazone-(3) of the formula:—



in the form of white crystals melting at 226—227°C.

What we claim is:—

1. A process for the manufacture of pyridazone-(3) compounds, wherein a hydrazine which contains at least three hydrogen atoms attached to the nitrogen atoms is condensed directly or in stages with two components, namely (a) an organic α-dicarbonyl compound or a reactive functional carbonyl mono- or di-derivative thereof as described hereinbefore and (b) an organic carboxylic acid of which the carbon grouping in the α-position is a reactive methylene group or a reactive nitrogen-free functional derivative of such acid, ring closure being brought about by the use of a basic condensing agent with the formation of a pyridazone-(3) compound, and if desired, a resulting compound having a functionally converted carboxyl group in 4-position as described hereinbefore is hydrolysed to the free acid and/or, if desired, a free carboxylic acid group in 4-position is decarboxylated and/or a resulting pyridazone-(3) having a hydrogen atom at the ring nitrogen atom in 2-position is, if desired, alkylated and/or, if desired, a base or acid so obtained is converted into a salt thereof.

2. A process as claimed in claim 1, wherein the organic α-dicarbonyl compound or a reactive functional carbonyl mono- or di-derivative thereof as described hereinbefore is reacted with the hydrazine to form a monohydrazone, and the latter is condensed with the organic carboxylic acid or reactive nitrogen-free functional derivative thereof with the use of a basic condensing agent.

3. A process as claimed in claim 1, wherein the organic carboxylic acid or reactive nitrogen-free functional derivative thereof is reacted with the hydrazine to form a carboxylic acid hydrazide, and the latter is condensed with the organic α-dicarbonyl compound or reactive functional carbonyl mono- or di-derivative thereof as described hereinbefore with the use of a basic condensing agent.

4. A process as claimed in claim 1, wherein all three of the reaction components are simultaneously present in the reaction.

5. A process as claimed in claim 2, wherein an acylmonohydrazone of an organic α-dicarbonyl compound resulting from the reaction of an organic α-dicarbonyl compound or a reactive functional carbonyl mono- or di-derivative thereof as described hereinbefore and a hydrazine which contains at least three hydrogen atoms attached to the nitrogen atoms is subjected to ring closure in the presence of a basic condensing agent.

6. A process as claimed in any one of claims 1—5, wherein an organic carboxylic acid containing an α-methylene group activated by a carbonyl, carboxyl, carbalkoxy or cyano group, or a reactive functional derivative of such acid, is used as starting material.

7. A process as claimed in claim 6, wherein an ester of an alkanol containing 1—5 carbon atoms with the said organic carboxylic acid is used.

8. A process as claimed in claim 7, wherein an acyl-acetic acid ester is used.

9. A process as claimed in claim 8, wherein an acetoacetic acid ester is used.

10. A process as claimed in claim 8, wherein a benzoyl-acetic acid ester is used.

11. A process as claimed in claim 7, wherein a cyan-acetic acid ester is used.

12. A process as claimed in claim 7, wherein a malonic acid diester is used.

13. A process as claimed in any one of claims 1—12, wherein hydrazine is used as starting material.

14. A process as claimed in any one of claims 1—12, wherein a phenylhydrazine is used as starting material.

15. A process as claimed in any one of claims 1—14, wherein a benzil is used as starting material.

16. A process as claimed in any one of claims 1—14, wherein diacetyl is used as starting material.

17. A process as claimed in any one of

claims 1—14, wherein benzoylacetyl is used as starting material.

18. A process as claimed in any one of claims 1—14, wherein a reactive functional carbonyl mono- or di- derivative of glyoxal as described hereinbefore is used as starting material.

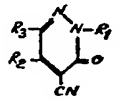
19. A process as claimed in any one of claims 1—14, wherein an ortho-quinone is used as starting material.

20. A modification of the process claimed in either of claims 2 and 3, wherein a compound obtainable as an intermediate product in the said process is used as starting material and the remaining stages of the process are carried out.

21. A process for the manufacture of a pyridazone compound conducted substantially as described in any one of the Examples 1—41 and 43 herein.

22. Pyridazone-(3)-compounds which contain a cyano group in the 4-position.

23. Pyridazone - (3) - compounds of the formula



in which R_1 represents hydrogen, a phenyl or halogeno-phenyl residue or a lower alkyl residue containing 1—5 carbon atoms, and R_2 and R_3 represent phenyl or halogeno-phenyl residues or lower alkyl residues containing 1—5 carbon atoms.

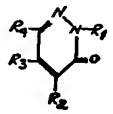
24. 2:5:6-Tri - lower alkyl-4-cyano-pyridazones-(3) in which the lower alkyl residues contain 1—5 carbon atoms.

25. 2:5:6 - Trimethyl - 4 - cyano - pyridazone-(3).

26. 5:6-Dimethyl-4-cyano-pyridazone-(3).

27. 4-Cyano-pyridazone-(3).

28. Pyridazone-(3)-compounds of the formula.



in which R_1 represents hydrogen, a phenyl or halogeno-phenyl residue or lower alkyl residue containing 1—5 carbon atoms, R_2 represents a free or esterified carboxyl group or an acetyl group, and each of the residues R_3 and R_4 represents a phenyl or halogeno-phenyl residue or a lower alkyl residue containing 1—5 carbon atoms or R_3 represents hydrogen or a lower alkyl residue containing 1—5 carbon atoms and R_4 hydrogen.

29. 2-Methyl - 4 - carboxy-5:6-diphenyl-pyridazone-(3).

30. 4-Carboxy-5:6 - diphenyl - pyridazone-(3).

31. 4:5:6-Triphenyl-pyridazone-(3).

32. 4-Benzoyl-5:6 - diphenyl - pyridazone-(3).

33. 4-Carboxy-5:6-dimethyl - pyridazone-(3).

34. 5:6-Bis-(para-chlorophenyl) - 4 - carboxy-pyridazone-(3).

35. Any one of the pyridazone-(3)-compounds described in Examples 1—3, 5, 7, 9, 12, 13, 14, 16, 20, 22, 25—27, 30, 32, 33, 35, 36, 37 and 40 herein.

36. Pyridazone-(3)-compounds, whenever made by the process claimed in any one of claims 1—21 herein.

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